EXHIBIT A

BIONPHARMA®

October 30, 2018

VIA FEDERAL EXPRESS

Silvergate Pharmaceuticals Inc.
Attn: Chief Executive Officer
6251 Greenwood Plaza Blvd.
Suite 101
Greenwood Village, CO 80111

Silvergate Pharmaceuticals Inc.
Attn: Chief Executive Officer
6724 Perimeter Loop Road
Suite 273
Dublin, OH 43017

Silvergate Pharmaceuticals Inc.
Attn: Chief Executive Officer
7400 West 110th Street
Suite 300
Overland Park, KS 66210

Silvergate Pharmaceuticals Inc.
Attn: Chief Executive Officer
5371 Gordon Way
Dublin, OH 43017

Confidential Notice: This Letter contains Bionpharma Inc.'s proprietary information. Bionpharma Inc. considers this information a trade secret. You are not authorized to append this Letter to any court pleading (unless under seal) or any other public disclosure. *See In Re Gabapentin Patent Litigation*, 312 F.Supp.2d 653, 667 (D. N.J. 2004); 21 C.F.R. 314.430(b)-(d); *Southwestern Energy v. Eickenhorst*, 955 F. Supp. 1078, 1085 (W.D. Ark. 1997), *aff'd*, 175 F.3d 1025 (8th Cir. 1999) (regarding the penalties for public disclosure of proprietary information); 18 U.S.C.A. 1832 (Federal Economic Espionage Act).

Re: Notice of Certification Under 21 U.S.C. § 355(j)(2)(B) (§ 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act) and 21 C.F.R. § 314.95

Dear Sir / Madam:

Pursuant to subsection 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act, ("the Act"), Bionpharma Inc. ("Bionpharma") is providing Notice of the following information to you, as the holder of New Drug Application (NDA) number N208686 for Enalapril Maleate (Epaned®) oral solution, 1 mg/mL, or as the patent owner and/or assignee thereof of the following patents: U.S. Patent Nos. 9,669,008 ("'008 patent"); 10,039,745 ("'745 patent"); and 9,808,442 ("'442 patent"), which are listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* ("Orange Book") associated with Epaned® (collectively "the Challenged Patents").

Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(I) and 21 C.F.R. §§ 314.95(c)(1), we advise you that the FDA has received an Abbreviated New Drug Application ("ANDA") from Bionpharma for Bionpharma's enalapril maleate oral solution, 1 mg/mL product ("the Bionpharma ANDA Product" or "Bionpharma's ANDA Product"). The ANDA contains the required bioavailability and/or bioequivalence data or waiver, as applicable. The ANDA was submitted under 21 U.S.C. §§ 355(j)(1) and (2)(A), and contains a Paragraph IV certification to obtain approval to engage in the commercial manufacture, use or sale of the Bionpharma ANDA Product, before the expiration of each of the Challenged Patents.

Pursuant to 21 C.F.R. § 314.95(c)(2), we advise you that the ANDA submitted by Bionpharma has been assigned the number 212408 by the FDA.

Pursuant to 21 C.F.R. § 314.95(c)(3), we advise you that Bionpharma has received the paragraph IV acknowledgement letter for the ANDA.

Pursuant to 21 C.F.R. § 314.95(c)(4), we advise you that the established name of the drug product that is the subject of Bionpharma's ANDA is enalapril maleate oral solution, 1 mg/mL.

Pursuant to 21 C.F.R. § 314.95(c)(5), we advise you that the active ingredient in the proposed drug product is known as enalapril maleate; the proposed strength is 1 mg/mL; and the proposed dosage form is an oral solution.

Pursuant to 21 C.F.R. § 314.95(c)(6), we advise you that the patents alleged to be invalid and/or not infringed in the Paragraph IV certification are the Challenged Patents, which are listed in the FDA's Orange Book in connection with NDA 208686 for Enalapril Maleate (Epaned®) solution, 1 mg/mL. According to the Orange Book, the Challenged Patents have the following expiration dates:[1]

Patent	Expiration Date
9,669,008	3/25/2036
10,039,745	3/25/2036
9,808,442	3/25/2036

Pursuant to 21 C.F.R. §§ 314.95(a) and 314.95(g), service of this notice letter and detailed statement is effectuated by a "designated delivery service."

Bionpharma alleges, and has certified to the FDA, that in Bionpharma's opinion and to the best of its knowledge, the Challenged Patents are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the drug product described in Bionpharma's ANDA. Therefore, pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(7), Bionpharma's detailed statement of the legal and factual basis for the Paragraph IV certification with respect to each of the Challenged Patents is attached hereto and made a part hereof.

Bionpharma reserves the right to assert additional factual and legal bases concerning non-infringement, invalidity, or unenforceability should future information so warrant.

The Offer of Confidential Access as provided by 21 U.S.C. § 355(j)(5)(C)(i)(III) and 21 C.F.R. § 314.95(c)(8) is attached to this Notice Letter.

Service of Process and Courtesy Copies:

The following person is authorized to accept service of process for any patent infringement complaint that may result from this notification (and limited to such a complaint only):

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[1] Bionpharma does not aver that these expiration dates are correct.

BIONPHARMA®

Brian P. Murray, Esq.
Taft, Stettinius & Hollister LLP
111 East Wacker Drive, Suite 2800
Chicago, IL 60601

Reservation of Legal Rights:

Bionpharma reserves the right to assert the same, similar, different or new theories of non-infringement, invalidity and/or unenforceability and nothing in this Notice Letter or Detailed Statement shall be construed as to limit Bionpharma's right to make any allegation in any subsequent litigation regarding any issue.

Yours very truly,

Bionpharma Inc.

Usha Sankaran, Associate Vice President, Regulatory Affairs
Bionpharma Inc.
600 Alexander Rd.
Suite 2-4B
Princeton, NJ 08540
Tel.: 1 609-380-3321
Fax: 1 609-380-3311

I. Detailed Statement for ANDA No. 212408

A. Introduction.

Pursuant to 21 U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6), this document is the detailed statement of the factual and legal bases for the paragraph IV certification of Bionpharma that, in its opinion and to the best of its knowledge, the claims of U.S. Patent Nos. 9,669,008 ("'008 patent"); 10,039,745 ("'745 patent"); and 9,808,442 ("'442 patent") are invalid, unenforceable and/or will not be infringed by the commercial manufacture, use or sale of the drug product described in Bionpharma's ANDA 212408. Bionpharma reserves the right to raise additional factual and legal bases concerning non-infringement, invalidity, and/or unenforceability in any litigation or other proceeding that may result from receipt of this letter.

A.1 Bionpharma's ANDA Product.

Bionpharma's ANDA Product is an oral solution containing enalapril maleate as the active ingredient. The strength of the proposed ANDA product is 1 mg/mL.

B. Legal Standards.

B.1 Claim Construction.

It is a "bedrock principle" of patent law that "the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005). The first step, claim construction, "is simply a way of elaborating the normally terse claim language in order to understand and explain, but not to change, the scope of the claims." *DeMarini Sports, Inc. v. Worth, Inc.,* 239 F.3d 1314, 1322 (Fed. Cir. 2001) (citation omitted); *see also*, *Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1273 (Fed. Cir. 2004).

The words of a claim "are generally given their ordinary and customary meaning," *i.e.*, the meaning that the term would have to a person of ordinary skill in the art in question as of the effective filing date of the patent application. *Phillips*, 415 F.3d at 1312-13 (citations omitted); *see also*, *Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1370 (Fed. Cir. 2005). Because the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent, and because patentees frequently use terms idiosyncratically, courts look to "those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean," which include "the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Phillips*, 415 F.3d at 1314 (citations omitted).

When construing a patent claim, a court first analyzes the intrinsic evidence of record—the claims, the specification, and the prosecution history, as such evidence is the most significant source of the legally operative meaning of a claim. *See Phillips*, 415 F.3d at 1314-17; *Markman v. Westview Instruments Inc.,* 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996). While "words in a claim are generally given their ordinary and customary meaning, a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is clearly stated in the patent

specification or file history." *Vitronics Corp. v. Conceptronic, Inc.,* 90 F.3d 1576, 1582 (Fed. Cir. 1996); *see Phillips*, 415 F.3d at 1316; *see also, Anderson Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1370 (Fed. Cir. 2007); *3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F. 3d 12365, 1374 (Fed. Cir. 2003); *AIA Eng'g, Ltd. V. Magotteaux Inter., S/A*, 657 F. 3d 1264, 1276 (Fed. Cir. 2011).

The Federal Circuit has recognized that a court construing a patent claim may also utilize extrinsic evidence, such as expert testimony and technical dictionaries. *Phillips*, 415 F.3d at 1317. While extrinsic evidence on the issue of claim construction may be referenced, the Federal Circuit has held that it is "less significant than the intrinsic record in determining 'the legally operative meaning of claim language.'" *Id*. On several occasions, the Federal Circuit has admonished courts construing patent claims for relying on extrinsic evidence because it "poses the risk that [the extrinsic evidence] will be used to change the meaning of claims in derogation of the 'indisputable public records consisting of the claims, the specification and the prosecution history,' thereby undermining the public notice function of patents." *Id*. at 1319 (citation omitted). Likewise, extrinsic evidence may not correct errors, erase limitations, or otherwise diverge from the description of the invention as contained in the patent documents. *Aqua-Aerobic Sys., Inc. v. Aerators, Inc.*, 211 F.3d 1241, 1245 (Fed. Cir. 2000).

A patentee cannot recapture in litigation claim scope surrendered, either by amendment or argument, during the prosecution of the patent. *See Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.,* 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). Because "[c]laims may not be construed one way in order to obtain their allowance and in a different way against accused infringers," *Southwall Techs., Inc. v. Cardinal IG Co.,* 54 F.3d 1570, 1576 (Fed. Cir. 1995), *cert denied*, 516 U.S. 987 (1995), if a claim must be construed in a particular way to make the claimed subject matter patentable, it cannot be construed differently to cover an accused device if that construction would simultaneously include the prior art. This principle prevents a patentee from claiming that its patent claims cover subject matter for which the PTO was unwilling to issue a patent. It also gives courts guidance as to what claims or claim elements warrant a narrow scope. When a patentee urges a court to broadly construe or effectively "read out" claim limitations which, if so broadly construed or eliminated, would fail to differentiate a claim from the prior art, courts have a basis for rejecting such claim constructions. *See id.* at 1580-82; *see DeMarini,* 239 F.3d at 1332.

The Supreme Court set aside the Federal Circuit's *de novo* review of every aspect of a lower court's claim construction decision, rejecting that form of review where the district court has resolved factual disputes and made factual findings about the extrinsic evidence. *Teva Pharm. USA, Inc. v. Sandoz, Inc.,* 135 S. Ct. 831, 841 (2015). The Supreme Court held that the "clear error" standard of review applies in those circumstances. *Id.* However, it also confirmed that the "ultimate" construction of the claim, even where underlying factual disputes have been resolved, remains a legal conclusion that the Federal Circuit can review *de novo*. *Id* at 834. The Court also confirmed that *de novo* review is appropriate in cases where the district court reviews only evidence intrinsic to the patent. *Id.*

B.2. Infringement Analysis.

The first step to determining whether infringement exists is to construe the patent claim language. Second, the properly construed claims are compared to the accused product or process to determine whether it falls within the scope of the claims. *Markman*, 52 F.3d at 976; *Dynacore*, 363 F.3d at 1273.

Literal infringement of a patent claim requires that the accused product contain each limitation of the claim; if one or more limitations or their equivalent cannot be found in the accused product or process, the claim is not infringed (e.g. "all elements rule"). *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538-39 (Fed. Cir. 1991); *Cross Med. Prods. v. Medtronic Sofamor Danek*, 424 F.3d 1293, 1309-11 (Fed. Cir. 2005). If the accused product lacks even a single claim element, there is no literal infringement. *V-Formation, Inc. v. Benetton Grp. SpA*, 401 F.3d 1307, 1312 (Fed. Cir. 2005).

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.,* 520 U.S. 17, 29 (1997). Two primary approaches have been used for determining equivalents: (1) the "triple identity" approach; and (2) the "insubstantial differences" approach. The triple identity approach focuses on whether the substitute element of the accused product or process performs substantially the same function, in substantially the same way, to achieve substantially the same result as the claim limitation for which equivalence is at issue (e.g., "Function-Way-Result" test). *Id.* at 39; *Crown Packaging Tech., Inc. v. Rexam Beverage Can Co.*, 559 F.3d 1308, 1312 (Fed. Cir. 2009). The insubstantial differences approach focuses on "whether the substitute element plays a role substantially different from the claimed element." *Id.* at 40. In the chemical arts, the insubstantial differences test general is more suitable than the Function-Way-Result test for evaluating infringement under the doctrine of equivalents. *See Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 867 (Fed. Cir. 2017).

Further, "the concept of equivalency cannot embrace a structure that is specifically excluded from the scope of the claims." *Dolly, Inc. v. Spalding & Evenflo Cos., Inc.,* 16 F.3d 394, 400 (Fed. Cir. 1994). Once a patent issues, all limitations in a claim are material and must be met in the accused device or method – either exactly or equivalently. *See Becton Dickinson & Co. v. C.R. Bard Inc.,* 922 F.2d 792, 798 (Fed. Cir. 1990). "There can be no infringement as a matter of law if a claim limitation is totally missing from the accused device." *London,* 946 F.2d at 1539; *Cross Med.*, 424 F.3d at 1309-11. "The doctrine of equivalents cannot be used to erase meaningful structural and functional limitations of the claim on which the public is entitled to rely in avoiding infringement." *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556, 1562 (Fed. Cir. 1994), *cert. denied*, 514 U.S. 1078 (1995). "It is important to insure that the application of the doctrine [of equivalents], even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety." *Warner-Jenkinson*, 520 U.S. at 29; *see Cooper Cameron Corp. v. Kvaerner Oilfield Prods., Inc.*, 291 F.3d 1317, 1321-22 (Fed. Cir. 2002) (There can be no infringement under the doctrine of equivalents when a limitation of a claim is missing—the claim required a port to be positioned "between" two plugs so there was no infringement by equivalents where the accused positioned the port "above" the two plugs). The scope of equivalents also may not encompass the prior art. *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990), *disapproved of on other grounds by Cardinal Chem. Co. v. Morton Int'l, Inc.*, 508 U.S. 83 (1993) ("[S]ince prior art

always limits what an inventor could have claimed, it limits the range of permissible equivalents of a claim.").

The patentee, as the author of the claim language, may be expected to draft claims encompassing readily known equivalents. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 740 (2002). A patentee who narrows a claim by amendment during prosecution to satisfy a requirement of the Patent Act is presumed to have surrendered any equivalents in the territory between the original claim and the amended claim. *Id.*; *see Deering Precision Instruments, L.L.C. v. Vector Distribution Sys., Inc.*, 347 F.3d 1314, 1325 (Fed. Cir. 2003); *Ranbaxy Pharm. Inc. v. Apotex, Inc.,* 350 F.3d 1235, 1241 (Fed. Cir. 2003). The presumption can be overcome if the equivalent was unforeseeable at the time of the application, the rationale underlying the amendment bears no more than a tangential relationship to the equivalent in question, or there was some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question. *Ranbaxy Pharm.*, 350 F.3d at 1241 (*citing and quoting in part, Festo Corp.,* 535 U.S. at 740-41). The question of whether the presumption has been rebutted is a question of law for a court.

Prosecution history estoppel is premised upon the notion that "a patentee should not be able to obtain, through litigation, coverage of subject matter relinquished during prosecution." *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1424 (Fed. Cir. 1994). A patentee is estopped from recapturing coverage relinquished by argument or amendment during prosecution by application of the doctrine of equivalents. *See Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1564 (Fed. Cir. 1990), *cert. dismissed*, 499 U.S. 955 (1991); *Southwall Techs.,* 54 F.3d at 1582-84; *Canton Bio-Medical, Inc. v. Integrated Liner Techs., Inc.*, 216 F.3d 1367, 1371 (Fed. Cir. 2000) (patentee was barred from asserting that a single prior art component was an equivalent where the patentee had argued that its invention was a "particular primer solution" distinguished by its use of three specific components from the prior art); *PODS, Inc. v. Porta Stor, Inc.*, 484 F.3d 1359, 1368 (Fed. Cir. 2007), *cert denied*, 522 U.S. 1022 (2007) (arguments made to distinguish prior art as lacking a rectangular-shaped frame created a clear and unmistakable surrender of coverage for frames that were not rectangular or four-sided); *see also*, *Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270, 1277 (Fed. Cir. 2012); *Typhoon Touch Techs., Inc. v. Dell, Inc.*, 659 F.3d 1376 (Fed. Cir. 2011).

"To invoke argument-based estoppel … the prosecution history must evince a clear and unmistakable surrender of subject matter." *PODS*, 484 F.3d at 1367. Clear assertions made in support of patentability may create an estoppel, regardless of whether or not they were actually required for allowance of a claim. *Id*. at 1368. The relevant inquiry is "whether a competitor would reasonably believe that the applicant had surrendered the relevant subject matter." *Id*. Once an argument-based estoppel is created with regard to a claim term, the estoppel applies to that term in other claims. *Id*.

C. The Orange Book Patent with a Paragraph IV Certification.

C.1. U.S. Patent No. 9,669,008.

The '008 patent, entitled "ENALAPRIL FORMULATIONS," is directed to enalapril oral liquid formulations. ('008 patent at Abstract). The '008 patent issued on June 6, 2017 from U.S.

Patent Application Serial No. 15/081,603 ("'603 application"), filed on March 25, 2016, which claims priority to Provisional Application No. 62/310,198, filed on March 18, 2016. According to the FDA's Electronic Orange Book, the '008 patent expires on March 25, 2036. According to the USPTO electronic assignment database, the '008 patent is assigned to Silvergate Pharmaceuticals, Inc.

The '008 patent lists Gerold L. Mosher and David W. Miles as inventors.

The '008 patent discloses and claims stable enalapril oral liquid formulation.

C.1.1. The Claims of the '008 Patent.

The '008 patent issued with 20 claims set forth below:

> 1. A stable oral liquid formulation, comprising:
>
> (i) about 1 mg/ml enalapril maleate;
>
> (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate;
>
> (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
>
> (iv) water;
>
> wherein the pH of the formulation is less than about 3.5; and
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months;
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
>
> 2. The formulation of claim 1, further comprising a flavoring agent.
>
> 3. The formulation of claim 1, wherein the pH is between about 3 and about 3.5.
>
> 4. The formulation of claim 3, wherein the pH is about 3.3.
>
> 5. The formulation of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

6. The formulation of claim 5, wherein the citrate concentration in the buffer is about 10 mM.

7. The formulation of claim 1, wherein the formulation is stable at about 5±3° C. for at least 18 months.

8. The formulation of claim 1, wherein the formulation is stable at about 5±3° C. for at least 24 months.

9. The formulation of claim 1, wherein the formulation does not contain mannitol.

10. The formulation of claim 1, wherein the formulation does not contain silicon dioxide.

11. A stable oral liquid formulation, comprising:

(i) about 19.3% (w/w of solids) enalapril maleate;

(ii) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate;

(iii) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and

(iv) water;

wherein the pH of the formulation is less than about 3.5; and

wherein the formulation is stable at about 5±3° C. for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

12. The formulation of claim 11, further comprising a flavoring agent.

13. The formulation of claim 11, wherein the pH is between about 3 and about 3.5.

14. The formulation of claim 13, wherein the pH is about 3.3.

15. The formulation of claim 11, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

16. The formulation of claim 15, wherein the citrate concentration in the buffer is about 10 mM.

17. The formulation of claim 11, wherein the formulation is stable at about 5±3° C. for at least 24 months.

18. A stable oral liquid formulation, consisting essentially of:

(i) about 1 mg/ml enalapril maleate;

(ii) about 0.70 mg/ml of a sweetener that is sucralose;

(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;

(iv) about 1 mg/ml of a preservative that is sodium benzoate;

(v) a flavoring agent; and

(vi) water;

wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and

wherein the formulation is stable at about 5±3° C. for at least 12 months;

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

19. The stable oral liquid formulation of claim 1, further comprising about 0.70 mg/ml of a sweetener that is sucralose.

20. The stable oral liquid formulation of claim 11, further comprising about 13.5% (w/w of solids) of a sweetener that is sucralose.

C.1.2. There is No Infringement of Any Claims by the Bionpharma ANDA Product.

The commercial manufacture, use, sale, and/or offer for sale of the Bionpharma ANDA Product will not infringe any valid claim of the '008 patent either literally or under the doctrine of equivalents.

C.1.2.1. Claim 1 is Not Infringed by the Bionpharma ANDA Product.

Claim 1 requires:

> 1. A stable oral liquid formulation, comprising:
>
> (i) about 1 mg/ml enalapril maleate;
>
> (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate;
>
> (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
>
> (iv) water;
>
> wherein the pH of the formulation is less than about 3.5; and
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months;
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

C.1.2.1.1. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate."

The Bionpharma ANDA Product does not contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate" as required by claim 1 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.1.2.1.2. The Bionpharma ANDA Product Does Not Contain "about 1 mg/ml of a preservative that is sodium benzoate."

The Bionpharma ANDA Product does not contain "about 1 mg/ml of a preservative that is sodium benzoate" as required by claim 1 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused

product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product does not contain two separate required elements of claim 1 of the '008 patent and, thus, cannot infringe claim 1 of the '008 patent.

C.1.2.2. Claims 2-10 and 19 are Not Infringed by the Bionpharma ANDA Product.

Claims 2-10 and 19 of the '008 patent depend, directly or indirectly, from independent claim 1. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 1 of the '008 patent will not be infringed by the Bionpharma ANDA Product. Therefore, dependent claims 2-10 and 19 of the '008 patent will not be infringed by the Bionpharma ANDA Product.

C.1.2.3. Claim 11 is Not Infringed by the Bionpharma ANDA Product.

Claim 11 requires:

> 1. A stable oral liquid formulation, comprising:
>
> (i) about 19.3% (w/w of solids) enalapril maleate;
>
> (ii) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate;
>
> (iii) about 19.3% (w/w of solids) of a preservative that is sodium benzoate; and
>
> (iv) water;
>
> wherein the pH of the formulation is less than about 3.5; and
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months;
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

C.1.2.3.1. The Bionpharma ANDA Product Does Not Contain "about 19.3% (w/w of solids) enalapril maleate."

The Bionpharma ANDA Product does not contain "about 19.3% (w/w of solids) enalapril maleate" as required by claim 11 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.1.2.3.2. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate."

The Bionpharma ANDA Product does not contain "a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate" as required by claim 11 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.1.2.3.3. The Bionpharma ANDA Product Does Not Contain "about 19.3% (w/w of solids) of a preservative that is sodium benzoate."

The Bionpharma ANDA Product does not contain "about 19.3% (w/w of solids) of a preservative that is sodium benzoate" as required by claim 11 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product does not contain three separate required elements of claim 11 of the '008 patent, and thus, cannot infringe claim 11 of the '008 patent.

C.1.2.4. Claims 12-17 and 20 are Not Infringed by the Bionpharma ANDA Product.

Claims 12-17 and 20 of the '008 patent depend, directly or indirectly, from independent claim 11. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 11 of the '008 patent will be

infringed by the Bionpharma ANDA Product. Therefore, dependent claims 12-17 and 20 of the '008 patent will not be infringed by the Bionpharma ANDA Product.

C.1.2.5. Claim 18 is Not Infringed by the Bionpharma ANDA Product.

Claim 18 requires:

> 1. A stable oral liquid formulation, consisting essentially of:
>
> (i) about 1 mg/ml enalapril maleate;
>
> (ii) about 0.70 mg/ml of a sweetener that is sucralose;
>
> (iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;
>
> (iv) about 1 mg/ml of a preservative that is sodium benzoate;
>
> (v) a flavoring agent; and
>
> (vi) water;
>
> wherein the pH of the formulation is less than about 3.5 adjusted by sodium hydroxide or hydrochloric acid if needed; and
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months;
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

C.1.2.5.1. The Bionpharma ANDA Product Does Not Contain "about 0.70 mg/ml of a sweetener that is sucralose."

The Bionpharma ANDA Product does not contain "about 0.70 mg/ml of a sweetener that is sucralose" as required by claim 18 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.1.2.5.2. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate."

The Bionpharma ANDA Product does not contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" as required by claim 18 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.1.2.5.3. The Bionpharma ANDA Product Does Not Contain "about 1 mg/ml of a preservative that is sodium benzoate."

The Bionpharma ANDA Product does not contain "about 1 mg/ml of a preservative that is sodium benzoate" as required by claim 18 of the '008 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product independently fails to contain three separate required elements of claim 18 of the '008 patent, and thus, cannot infringe claim 18 of the '008 patent.

C.1.2.6. Claims 1-10 and 19 are Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claims 1-10 and 19 of the '008 patent all require at least (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate. As discussed above, the Bionpharma ANDA Product does not contain any of (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate. Nor does the Bionpharma ANDA Product contain an equivalent of any of (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe any of claims 1-10 and 19 of the '008 patent under the doctrine of equivalents.

C.1.2.6.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.1.2.6.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH, 2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims***.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In

contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '008 patent.

C.1.2.6.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate" and "about 1 mg/ml of a preservative that is sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

C.1.2.7. Claims 11-17 and 20 are Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claims 11-17 and 20 of the '008 patent all require at least (a) about 19.3% (w/w of solids) enalapril maleate; (b) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate; and (c) about 19.3% (w/w of solids) of a preservative that is sodium benzoate. As discussed above, the Bionpharma ANDA Product does not comprise any of (a) about 19.3% (w/w of solids) enalapril maleate; (b) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate; and (c) about 19.3% (w/w of solids) of a preservative that is sodium benzoate. Nor does the Bionpharma ANDA Product comprise an equivalent of any of (a) about 19.3% (w/w of solids) enalapril maleate; (b) a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate; and (c) about 19.3% (w/w of solids) of a preservative that is sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe any of claims 11-17 and 20 of the '008 patent under the doctrine of equivalents.

C.1.2.7.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.1.2.7.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH,

2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims***.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '008 patent.

C.1.2.7.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "about 19.3% (w/w of solids) enalapril maleate," "a buffer comprising about 35.2% (w/w of solids) citric acid and about 2.9% (w/w of solids) sodium citrate dihydrate," and "about 19.3% (w/w of solids) of a preservative that is sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

C.1.2.8. Claim 18 is Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claim 18 of the '008 patent requires at least (a) about 0.70 mg/ml of a sweetener that is sucralose; (b) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and (c) about 1 mg/ml of a preservative that is sodium benzoate. As discussed above, the Bionpharma ANDA Product does not comprise any of about 1 mg/ml of a preservative that is sodium benzoate. Nor does the Bionpharma ANDA Product comprise an equivalent of any of about 1 mg/ml of a preservative that is sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe claim 18 of the '008 patent under the doctrine of equivalents.

C.1.2.8.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.1.2.8.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH, 2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims***.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate,***

sucralose and water at the recited concentrations and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '008 patent.

C.1.2.8.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "about 0.70 mg/ml of a sweetener that is sucralose," "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate," and "about 1 mg/ml of a preservative that is sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

C.1.2.9. Claims 1-20 are Not Indirectly Infringed by the Bionpharma ANDA Product.

Liability for either inducement of infringement or contributory infringement requires direct infringement by another as a prerequisite (i.e., the performance of all the patent's steps that are "attributable to one person"). *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014) ("[T]here has simply been no infringement of the method . . . because the performance of all the patent's steps is not attributable to any one person. And, as both the Federal Circuit and respondents admit, where there has been no direct infringement, there can be no inducement of infringement under §271(b).").

As discussed above, there is no direct infringement of any claim of the '008 patent. Thus, Bionpharma cannot indirectly infringe any claim of the '008 patent.

* * * * *

As discussed above, Bionpharma cannot and does not infringe any claim of the '008 patent, directly or indirectly, literally or under the doctrine of equivalents.

C.2. U.S. Patent No. 10,039,745.

The '745 patent, entitled "ENALAPRIL FORMULATIONS," is directed to enalapril oral liquid formulations. ('745 patent at Abstract). The '745 patent issued on August 7, 2018 from U.S. Patent Application Serial No. 15/802,341 ("'341 application"), filed on November 2, 2017, which is a continuation of application no. 15/613,622, which is a continuation of application no. 15/081,603, which claims priority to Provisional Application No. 62/310,198, filed on March 18,

2016. According to the FDA's Electronic Orange Book, the '745 patent expires on March 25, 2036. According to the USPTO electronic assignment database, the '745 patent is assigned to Silvergate Pharmaceuticals, Inc.

The '745 patent lists Gerold L. Mosher and David W. Miles as inventors.

The '745 patent discloses and claims stable enalapril oral liquid formulation.

C.2.1. The Claims of the '745 Patent.

The '745 patent issued with 20 claims set forth below:

> 1. A stable oral liquid formulation, comprising:
>
> (i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;
>
> (ii) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate;
>
> (iii) about 0.7 to about 1.2 mg/ml sodium benzoate; and
>
> (iv) water;
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months; and
>
> wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.
>
> 2. The stable oral liquid formulation of claim 1 further comprising about 0.5 to about 0.9 mg/ml sucralose.
>
> 3. The stable oral liquid formulation of claim 1 further comprising a flavoring agent.
>
> 4. The stable oral liquid formulation of claim 1, wherein the formulation does not contain mannitol.
>
> 5. The stable oral liquid formulation of claim 1, wherein the formulation does not contain silicon dioxide.
>
> 6. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is less than about 3.5.

7. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

8. The stable oral liquid formulation of claim 1, wherein the pH of the stable oral liquid formulation is about 3.3.

9. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about 5±3° C. for at least 18 months.

10. The stable oral liquid formulation of claim 1, wherein the formulation is stable at about 5±3° C. for at least 24 months.

11. A stable oral liquid formulation, comprising:

(i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate;

(iii) about 3% to about 25% (w/w of solids) sodium benzoate; and

(iv) water;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

12. The stable oral liquid formulation of claim 11 further comprising about 8% to about 18% (w/w of solids) sucralose.

13. The stable oral liquid formulation of claim 11 further comprising a flavoring agent.

14. The stable oral liquid formulation of claim 11, wherein the formulation does not contain mannitol.

15. The stable oral liquid formulation of claim 11, wherein the formulation does not contain silicon dioxide.

16. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is less than about 3.5.

17. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is between about 3 and about 3.5.

18. The stable oral liquid formulation of claim 11, wherein the pH of the stable oral liquid formulation is about 3.3.

19. The stable oral liquid formulation of claim 11, wherein the formulation is stable at about 5±3° C. for at least 18 months.

20. The stable oral liquid formulation of claim 11, wherein the formulation is stable at about 5±3° C. for at least 24 months.

C.2.2. There is No Infringement of Any Claims by the Bionpharma ANDA Product.

The commercial manufacture, use, sale, and/or offer for sale of the Bionpharma ANDA Product will not infringe any valid claim of the '745 patent either literally or under the doctrine of equivalents.

C.2.2.1. Claim 1 is Not Infringed by the Bionpharma ANDA Product.

Claim 1 requires:

1. A stable oral liquid formulation, comprising:

(i) about 0.6 to about 1.2 mg/ml enalapril or a pharmaceutically acceptable salt or solvate thereof;

(ii) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate;

(iii) about 0.7 to about 1.2 mg/ml sodium benzoate; and

(iv) water;

wherein the formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5%

> w/w or less total impurity or related substances at the end of the given storage period.

C.2.2.1.1. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate."

The Bionpharma ANDA Product does not contain "a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate" as required by claim 1 of the '745 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.2.2.1.2. The Bionpharma ANDA Product Does Not Contain "about 0.7 to about 1.2 mg/ml sodium benzoate."

The Bionpharma ANDA Product does not contain "about 0.7 to about 1.2 mg/ml sodium benzoate" as required by claim 1 of the '745 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product independently fails to contain two separate required elements of claim 1 of the '745 patent, and thus, cannot infringe claim 1 of the '745 patent.

C.2.2.2. Claims 2-10 are Not Infringed by the Bionpharma ANDA Product.

Claims 2-10 of the '745 patent depend, directly or indirectly, from independent claim 1. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 1 of the '745 patent will be infringed by the Bionpharma ANDA Product. Therefore, dependent claims 2-10 of the '745 patent will not be infringed by the Bionpharma ANDA Product.

C.2.2.3. Claim 11 is Not Infringed by the Bionpharma ANDA Product.

Claim 11 requires:

> 1. A stable oral liquid formulation, comprising:

> (i) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof;
>
> (ii) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate;
>
> (iii) about 3% to about 25% (w/w of solids) sodium benzoate; and
>
> (iv) water;
>
> wherein the formulation is stable at about 5±3° C. for at least 12 months; and
>
> wherein the stable oral liquid formulation has about 95% w/w or greater of the initial enalapril amount and about 5% w/w or less total impurity or related substances at the end of the given storage period.

C.2.2.3.1. The Bionpharma ANDA Product Does Not Contain "about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof."

The Bionpharma ANDA Product does not contain "about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof" as required by claim 11 of the '745 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.2.2.3.2. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate."

The Bionpharma ANDA Product does not contain "a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate" as required by claim 11 of the '745 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.2.2.3.3. The Bionpharma ANDA Product Does Not Contain "about 3% to about 25% (w/w of solids) sodium benzoate."

The Bionpharma ANDA Product does not contain "about 3% to about 25% (w/w of solids) sodium benzoate" as required by claim 11 of the '745 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product independently fails to contain three separate required elements of claim 11 of the '745 patent, and thus, cannot infringe claim 11 of the '745 patent.

C.2.2.4. Claims 12-20 are Not Infringed by the Bionpharma ANDA Product.

Claims 12-20 of the '745 patent depend, directly or indirectly, from independent claim 11. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 11 of the '745 patent will be infringed by the Bionpharma ANDA Product. Therefore, dependent claims 12-20 of the '745 patent will not be infringed by the Bionpharma ANDA Product.

C.2.2.5. Claims 1-10 are Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claims 1-10 of the '745 patent all require at least (a) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; and (b) about 0.7 to about 1.2 mg/ml sodium benzoate. As discussed above, the Bionpharma ANDA Product does not comprise any of (a) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; and (b) about 0.7 to about 1.2 mg/ml sodium benzoate. Nor does the Bionpharma ANDA Product comprise an equivalent of any of (a) a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate; and (b) about 0.7 to about 1.2 mg/ml sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe any of claims 1-10 of the '745 patent under the doctrine of equivalents.

C.2.2.5.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application, a parent application to the '745 patent, were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric

acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.2.2.5.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the parent '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH, 2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims***.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations

compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '745 patent.

C.2.2.5.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "a buffer comprising about 0.8 to about 3.5 mg/ml citric acid and about 0.1 to about 0.8 mg/ml sodium citrate" and "about 0.7 to about 1.2 mg/ml sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

C.2.2.6. Claims 11-20 are Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claims 11-20 of the '745 patent all require at least (a) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof; (b) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium

citrate; and (c) about 3% to about 25% (w/w of solids) sodium benzoate. As discussed above, the Bionpharma ANDA Product does not comprise any of (a) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof; (b) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate; and (c) about 3% to about 25% (w/w of solids) sodium benzoate. Nor does the Bionpharma ANDA Product comprise an equivalent of any of (a) about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof; (b) a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate; and (c) about 3% to about 25% (w/w of solids) sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe any of claims 11-20 of the '745 patent under the doctrine of equivalents.

C.2.2.6.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application, a parent application to the '745 patent, were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.2.2.6.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the parent '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH, 2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite***

concentrations for a pharmaceutical liquid recited in the instant claims.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '745 patent.

C.2.2.6.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "about 10% to about 25% (w/w of solids) enalapril or a pharmaceutically acceptable salt or solvate thereof," "a buffer comprising about 17% to about 47% (w/w of solids) citric acid and about 1% to about 11% (w/w of solids) sodium citrate," and "about 3% to about 25% (w/w of solids) sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

C.2.2.7. Claims 1-20 are Not Indirectly Infringed by the Bionpharma ANDA Product.

Liability for either inducement of infringement or contributory infringement requires direct infringement by another as a prerequisite (i.e., the performance of all the patent's steps that are "attributable to one person"). *Limelight*, 134 S. Ct. at 2117 ("[T]here has simply been no infringement of the method . . . because the performance of all the patent's steps is not attributable to any one person. And, as both the Federal Circuit and respondents admit, where there has been no direct infringement, there can be no inducement of infringement under §271(b).").

As discussed above, there is no direct infringement of any claim of the '745 patent. Thus, Bionpharma cannot indirectly infringe any claim of the '745 patent.

* * * * *

As discussed above, Bionpharma cannot and does not infringe any claim of the '745 patent, directly or indirectly, literally or under the doctrine of equivalents.

C.3. U.S. Patent No. 9,808,442.

The '442 patent, entitled "ENALAPRIL FORMULATIONS," is directed to enalapril oral liquid formulations. ('442 patent at Abstract). The '442 patent issued on November 7, 2017 from U.S. Patent Application Serial No. 15/613,622 ("'622 application"), filed on June 5, 2017, which is a continuation of U.S. Patent Application No. 15/081,603, which claims priority to Provisional Application No. 62/310,198, filed on March 18, 2016. According to the FDA's Electronic Orange Book, the '442 patent expires on March 25, 2036. According to the USPTO electronic assignment database, the '442 patent is assigned to Silvergate Pharmaceuticals, Inc.

The '442 patent lists Gerold L. Mosher and David W. Miles as inventors.

The '442 patent discloses and claims methods of treating certain diseases through administration of a stable enalapril oral liquid formulation.

C.3.1. The Claims of the '442 Patent.

The '442 patent issued with 30 claims set forth below:

1. A method of treating hypertension in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising:

(i) about 1 mg/ml enalapril maleate;

(ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate;

(iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the pH of the stable oral liquid formulation is less than about 3.5;

wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

2. The method of claim 1, wherein the stable oral liquid formulation further comprises a flavoring agent.

3. The method of claim 1, wherein the stable oral liquid formulation further comprises about 0.70 mg/ml of a sweetener that is sucralose.

4. The method of claim 1, wherein the pH is between about 3 and about 3.5.

5. The method of claim 1, wherein the pH is about 3.3.

6. The method of claim 1, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

7. The method of claim 1, wherein the citrate concentration in the buffer is about 10 mM.

8. The method of claim 1, wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 18 months.

9. The method of claim 1, wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 24 months.

10. The method of claim 1, wherein the stable oral liquid formulation does not contain mannitol or silicon dioxide.

11. The method of claim 1, wherein the hypertension is primary (essential) hypertension.

12. The method of claim 1, wherein the hypertension is secondary hypertension.

13. The method of claim 1, wherein the subject has blood pressure values greater than or equal to 140/90 mmm Hg.

14. The method of claim 1, wherein the subject is elderly or a child.

15. The method of claim 1, wherein the stable oral liquid formulation is further administered in combination with an agent selected from the group consisting of diuretics, beta blockers, alpha blockers, mixed alpha and beta blockers, calcium channel blockers, angiotensin II receptor antagonists, ACE inhibitors, aldosterone antagonists, and alpha-2 agonists.

16. A method of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising:

(i) about 1 mg/ml enalapril maleate;

(ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and

(iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the pH of the stable oral liquid formulation is less than about 3.5;

wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 12 months; and

wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

17. The method of claim 16, wherein the stable oral liquid formulation further comprises about 0.70 mg/ml of a sweetener that is sucralose.

18. The method of claim 16, wherein the pH is between about 3 and about 3.5.

19. The method of claim 16, wherein the pH is between about 3.3.

20. The method of claim 16, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.

21. The method of claim 16, wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 24 months.

22. The method of claim 16, wherein the stable oral liquid formulation does not contain mannitol or silicon dioxide.

23. The method of claim 16, wherein the heart failure is congestive heart failure.

24. A method of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising:

(i) about 1 mg/ml enalapril maleate;

(ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and

(iii) about 1 mg/ml of a preservative that is sodium benzoate; and

(iv) water;

wherein the pH of the stable oral liquid formulation is less than about 3.5;

wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 12 months; and

> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.
>
> 25. The method of claim 24, wherein the stable oral liquid formulation further comprises about 0.70 mg/ml of a sweetener that is sucralose.
>
> 26. The method of claim 24, wherein the pH is between about 3 and about 3.5.
>
> 27. The method of claim 24, wherein the pH is between about 3.3.
>
> 28. The method of claim 24, wherein the citrate concentration in the buffer is about 5 mM to about 20 mM.
>
> 29. The method of claim 24, wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 24 months.
>
> 30. The method of claim 24, wherein the stable oral liquid formulation does not contain mannitol or silicon dioxide.

C.3.2. There is No Infringement of Any Claims by the Bionpharma ANDA Product.

The commercial manufacture, use, sale, and/or offer for sale of the Bionpharma ANDA Product will not infringe any valid claim of the '442 patent either literally or under the doctrine of equivalents.

C.3.2.1. Claims 1-15 Are Directed to Uses for which Bionpharma Is Not Seeking Approval.

Independent claim 1 is directed to a "method of treating hypertension in a subject." Claims 2-15 all depend directly on claim 1 and therefore incorporate all of the elements and limitations of independent claim 1. 35 U.S.C. § 112(d). Bionpharma is not seeking approval of its ANDA Product for the treatment of hypertension.

Because the labeling for Bionpharma's ANDA Product will include no instructions or promotion to use the Bionpharma ANDA Product for treatment of hypertension, Bionpharma will not be inducing infringement of claims 1-15. Moreover, there will be no direct infringement of claims 1-15—by Biopharma or any third parties who use Bionpharma's ANDA Product—because the formulation for Bionpharma's ANDA product will not contain all of the formulation elements recited in each of claims 1-15, as explained *supra*, with respect to the '008 patent, and *infra*, with respect to the remaining claims of the '442 patent. With no direct infringement, there can be no indirect infringement—either induced infringement or contributory infringement.

Thus, Bionpharma's ANDA Product and the use of same in accordance with Bionpharma's proposed label will not infringe claims 1-15, either directly or indirectly.

C.3.2.2. Claim 16 is Not Infringed by the Bionpharma ANDA Product.

Claim 16 requires:

> 16. A method of treating heart failure in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising:
>
> (i) about 1 mg/ml enalapril maleate;
>
> (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and
>
> (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
>
> (iv) water;
>
> wherein the pH of the stable oral liquid formulation is less than about 3.5;
>
> wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 12 months; and
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period..

C.3.2.2.1. Bionpharma Will Not Infringe the Method Element of Claim 16.

Bionpharma does not and cannot infringe the method elements of claim 16 of the '442 patent.

No Direct Infringement.

Claim 16 of the '442 patent requires "[a] method of treating … comprising administering … a therapeutically effective amount of a stable oral liquid formulation." Bionpharma does not directly administer medicines to patients in the United States for any use. Rather, only physicians may prescribe, only pharmacists may dispense, and only patients may directly administer Bionpharma's ANDA product in the United States for any particular therapeutic use. For at least this reason, Bionpharma would not directly literally infringe any method of use, which is required by all claims of the '442 patent. *Warner-Lambert*, 316 F.3d at 1363. Bionpharma would not directly infringe the '442 patent under the doctrine of equivalents either, because application of the doctrine here would require elimination of at least the "method of

treating … comprising administering … a therapeutically effective amount of a stable oral liquid formulation" limitations in violation of the all-elements rule. *Id.*

No Induced Infringement.

Inducing infringement under 35 U.S.C. § 271(b) requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard.*, 911 F.2d at 675. The patentee must prove that the defendant's "actions induced infringing acts and that [they] knew or should have known [their] actions would induce actual infringement." *Manville*, 917 F.2d at 553. Proof of mere knowledge of the acts alleged to constitute infringement is insufficient; specific intent and action to induce infringement must be proven. *DSU,* 471 F.3d at 1305. In the ANDA context, the Federal Circuit has made clear that the patentee must prove that the ANDA applicant will actually promote or encourage others, here pharmacists, nurses or other end users, to infringe the patent by using the drug for the patented use. *Warner-Lambert*, 316 F.3d at 1365. Moreover, intent to induce infringement cannot be inferred when there are substantial noninfringing uses for the drug. *Id.*; *see also Allergan*, 324 F.3d at 1332.

Because, as shown below, Bionpharma's ANDA product will not directly infringe the formulation elements of claim 16, there is no direct infringement by Bionpharma; as such, Bionpharma's proposed labeling will not mandate an infringing use by physicians or patients, there can be no inducement to infringe the claims of the '442 patent. *Joy Techs.*, 6 F.3d at 774 (stating that "[l]iability for . . . active inducement of infringement . . . is dependent upon the existence of direct infringement.").

Second, there is no evidence that Bionpharma will "promote or encourage others" to infringe the '442 patent by administering a product comprising either "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" or "about 1 mg/ml of a preservative that is sodium benzoate," as Bionpharma's ANDA product does not contain those ingredients, and thus no evidence of any specific intent on the part of Bionpharma.

No Contributory Infringement.

Contributory infringement under § 271(c) arises when there is a sale or offer for sale of a component of a patented apparatus or a material for use in a patented process if the material or apparatus constitutes a material part of the invention and the person supplying it knows that it is especially made for or especially adapted for use in an infringement of a patent. *See* 35 U.S.C. § 271(c). Judgment of non-infringement on a claim of contributory infringement is proper where the defendant proffers competent evidence that the product is used in a noninfringing manner. *See Alloc*, 342 F.3d at 1374 (affirming judgment of no contributory infringement where evidence was introduced that accused product could be used without infringing the claim).

Because, as shown below, there is no direct infringement by Bionpharma's ANDA product, Bionpharma cannot contribute to the infringement of the claims of the '442 patent by the manufacture, use or sale of Bionpharma's ANDA product. *Joy Techs.*, 6 F.3d at 774 ("[l]iability for … contributory infringement is dependent upon the existence of direct infringement.").

C.3.2.2.2. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" As Required by Claim 16.

The Bionpharma ANDA Product does not contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" as required by claim 16 of the '442 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.3.2.2.3. The Bionpharma ANDA Product Does Not Contain "about 1 mg/ml of a preservative that is sodium benzoate" As Required by Claim 16.

The Bionpharma ANDA Product does not contain "about 1 mg/ml of a preservative that is sodium benzoate" as required by claim 16 of the '442 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product does not contain two separate required elements of claim 16 of the '442 patent, and thus, cannot infringe claim 16 of the '442 patent.

C.3.2.3. Claims 17-23 are Not Infringed by the Bionpharma ANDA Product.

Claims 17-23 of the '442 patent depend, directly or indirectly, from independent claim 16. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 16 of the '442 patent will be infringed by the Bionpharma ANDA Product. Therefore, dependent claims 17-23 of the '442 patent will not be infringed by the Bionpharma ANDA Product.

C.3.2.4. Claim 24 is Not Infringed by the Bionpharma ANDA Product.

Claim 24 requires:

> 24. A method of treating left ventricular dysfunction in a subject comprising administering to that subject a therapeutically effective amount of a stable oral liquid formulation comprising:
>
> (i) about 1 mg/ml enalapril maleate;

> (ii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate; and
>
> (iii) about 1 mg/ml of a preservative that is sodium benzoate; and
>
> (iv) water;
>
> wherein the pH of the stable oral liquid formulation is less than about 3.5;
>
> wherein the stable oral liquid formulation is stable at about 5±3° C. for at least 12 months; and
>
> wherein the stable oral liquid formulation has about 95% or greater of the initial enalapril amount and about 5% w/w or less total impurities or related substances at the end of the given storage period.

C.3.2.4.1. Bionpharma Will Not Infringe the Method Element of Claim 24.

Bionpharma does not and cannot infringe the method elements of claim 24 of the '442 patent.

No Direct Infringement.

Claim 24 of the '442 patent requires "[a] method of treating … comprising administering … a therapeutically effective amount of a stable oral liquid formulation." Bionpharma does not directly administer medicines to patients in the United States for any use. Rather, only physicians may prescribe, only pharmacists may dispense, and only patients may directly administer Bionpharma's ANDA product in the United States for any particular therapeutic use. For at least this reason, Bionpharma would not directly literally infringe any method of use, which is required by all claims of the '442 patent. *Warner-Lambert*, 316 F.3d at 1363. Bionpharma would not directly infringe the '442 patent under the doctrine of equivalents either, because application of the doctrine here would require elimination of at least the "a] method of treating … comprising administering … a therapeutically effective amount of a stable oral liquid formulation" limitations in violation of the all-elements rule. *Id.*

No Induced Infringement.

Inducing infringement under 35 U.S.C. § 271(b) requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard.*, 911 F.2d at 675. The patentee must prove that the defendant's "actions induced infringing acts and that [they] knew or should have known [their] actions would induce actual infringement." *Manville*, 917 F.2d at 553. Proof of mere knowledge of the acts alleged to constitute infringement is insufficient; specific intent and action to induce infringement must be proven. *DSU,* 471 F.3d at 1305. In the ANDA context, the Federal Circuit has made clear that the patentee must prove that the ANDA applicant will actually promote or encourage others, here pharmacists, nurses or other end users, to infringe the patent by using the drug for the patented use. *Warner-Lambert*, 316 F.3d at 1365. Moreover,

intent to induce infringement cannot be inferred when there are substantial noninfringing uses for the drug. *Id*.; *see also Allergan*, 324 F.3d at 1332.

Because, as shown below, Bionpharma's ANDA product will not directly infringe the formulation elements of claim 24, there is no direct infringement by Bionpharma; as such, Bionpharma's proposed labeling will not mandate an infringing use by physicians or patients, there can be no inducement to infringe the claims of the '442 patent. *Joy Techs.*, 6 F.3d at 774 (stating that "[l]iability for . . . active inducement of infringement . . . is dependent upon the existence of direct infringement.").

Second, there is no evidence that Bionpharma will "promote or encourage others" to infringe the '442 patent by administering a product comprising either "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" or "about 1 mg/ml of a preservative that is sodium benzoate," as Bionpharma's ANDA product does not contain those ingredients, and thus no evidence of any specific intent on the part of Bionpharma.

No Contributory Infringement.

Contributory infringement under § 271(c) arises when there is a sale or offer for sale of a component of a patented apparatus or a material for use in a patented process if the material or apparatus constitutes a material part of the invention and the person supplying it knows that it is especially made for or especially adapted for use in an infringement of a patent. *See* 35 U.S.C. § 271(c). Judgment of non-infringement on a claim of contributory infringement is proper where the defendant proffers competent evidence that the product is used in a noninfringing manner. *See Alloc*, 342 F.3d at 1374 (affirming judgment of no contributory infringement where evidence was introduced that accused product could be used without infringing the claim).

Because, as shown below, there is no direct infringement by Bionpharma's ANDA product, Bionpharma cannot contribute to the infringement of the claims of the '442 patent by the manufacture, use or sale of Bionpharma's ANDA product. *Joy Techs.*, 6 F.3d at 774 ("[l]iability for … contributory infringement is dependent upon the existence of direct infringement.").

C.3.2.4.2. The Bionpharma ANDA Product Does Not Contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" As Required by Claim 24.

The Bionpharma ANDA Product does not contain "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/ml sodium citrate dihydrate" as required by claim 24 of the '442 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

C.3.2.4.3. The Bionpharma ANDA Product Does Not Contain "about 1 mg/ml of a preservative that is sodium benzoate" As Required by Claim 24.

The Bionpharma ANDA Product does not contain "about 1 mg/ml of a preservative that is sodium benzoate" as required by claim 24 of the '442 patent. Literal infringement requires a patentee to prove that every limitation of the asserted claim is literally met by the accused product. *Enercon*, 151 F.3d at 1384; *see also Amhil Enters.*, 81 F.3d at 1562 (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp.*, 939 F.2d at 1535.

* * *

The Bionpharma ANDA Product does not contain two separate required elements of claim 24 of the '442 patent, and thus, cannot infringe claim 24 of the '442 patent.

C.3.2.5. Claims 25-30 are Not Infringed by the Bionpharma ANDA Product.

Claims 25-30 of the '442 patent depend, directly or indirectly, from independent claim 24. A dependent claim incorporates all of the elements and limitations of the independent claim on which it depends. 35 U.S.C. § 112(d). Thus, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs*, 239 F.3d at 1310-11 & n.3. As discussed above, independent claim 24 of the '442 patent will be infringed by the Bionpharma ANDA Product. Therefore, dependent claims 25-30 of the '442 patent will not be infringed by the Bionpharma ANDA Product.

C.3.2.6. Claims 16-30 are Not Infringed by the Bionpharma ANDA Product under the Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the accused product to contain elements identical or equivalent to each claim limitation recited in a claim of a patent. *See Warner-Jenkinson,* 520 U.S. at 29.

Claims 16-30 of the '442 patent all require at least (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate. As discussed above, the Bionpharma ANDA Product does not comprise any of (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate. Nor does the Bionpharma ANDA Product comprise an equivalent of any of (a) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate; and (b) about 1 mg/ml of a preservative that is sodium benzoate.

Thus, the Bionpharma ANDA Product cannot infringe any of claims 16-30 of the '442 patent under the doctrine of equivalents.

C.3.2.6.1. Application of the Doctrine of Equivalents is Precluded by Amendment Based Prosecution History Estoppel.

The originally filed claims of the '603 application, a parent application to the '442 patent, were directed to an oral liquid formulation comprising (i) about 1 mg/ml enalapril maleate; (ii) about 0.70 mg/ml of a sweetener that is sucralose; (iii) a buffer comprising about 1.82 mg/ml citric

acid; (iv) about 1 mg/ml of a preservative that is sodium benzoate; and (v) water; wherein the pH of the formulation is less than about 3.5 and wherein the formulation is stable at about 5±3 °C for at least 12 months. ('008 Patent PH, Application at claims). In response to obviousness rejections by the PTO based on the prior art, Silvergate amended the claims to modify the claim from "(iii) a buffer comprising about 1.82 mg/ml citric acid" to "(iii) a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate." (*Id.* at Feb. 3, 2017 Amendment at 2-3). This amendment served to narrow the claims such that any subject matter lacking sodium citrate dihydrate, in the recited amount of 0.15 mg/mL, has been surrendered. Silvergate is estopped from recapturing any of the surrendered scope and asserting infringement against any pharmaceutical liquid lacking 0.15 mg/mL sodium citrate dihydrate.

C.1.2.6.2. Application of the Doctrine of Equivalents is Precluded by Argument Based Prosecution History Estoppel."

Silvergate is further estopped from asserting infringement under the doctrine of equivalents because of argument-based estoppel. Explicit disavowal can occur "when the patentee asserted the singularity or uniqueness of the claimed invention in arguing for its patentability." *Astrazeneca UK Ltd. v. Dr. Reddy's Labs., Ltd.*, No. 08-CV-3237 (MLC), 2010 WL 4721384, at *8 (D.N.J. Nov. 15, 2010). The Federal Circuit has held that argument-based estoppel applied in a case in which "the patentee had argued that 'only' the listed compound had the 'particular and novel' property that enabled the invention claimed." *Id.* (*quoting Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1313-14 (Fed. Cir. 2001)).

During prosecution of the parent '008 patent, Silvergate repeatedly argued that the exact formulation with all ingredients in very specific recited amounts were the unique aspect of its invention, and further disparaged and disclaimed other ingredients in other amounts. (*See, e.g.*, '008 Patent PH, 2/3/2017 Amendment/Req. Reconsideration at 7 ("Moreover, the cited references have not provided any reason to single out ***the specific components at the requisite concentrations for a pharmaceutical liquid recited in the instant claims***.") (emphasis added); *id.* at 12 ("The Citied References Also Do Not Teach ***the Claimed Combination of Components in the Present Enalapril Formulations***") (emphasis added); *id.* ("While these claimed ingredients and excipients may individually be disclosed in the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, ***none of these references teach or suggest the claimed combination of only enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and pH as stated in claim 20") (emphasis added); *id.* at 14 ("nothing in Nahata provides any reason or rationale of how one of ordinary skill in the art would use these teachings to arrive at the claimed stable enalapril oral liquid formulations, ***let alone pharmaceutical enalapril oral liquid formulations with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5") (emphasis added); *id.* at 16 ("While elements of the instant claims can be found scattered throughout these different references, there is no context or disclosure which brings forth these elements to the forefront and allows one to combine them successfully. Instead, each references discloses many other excipients that could potentially be used in equal measure."); *id.* at 16-17 (table comparing the excipients found in prior art to those of the claimed invention) (emphasis added); *id.* at 17 ("In contrast, ***the formulation of the present claims has only four ingredients along with enalapril and water***."); *id.* at 18 ("As such, the prior art does not provide any expectation that any particular combination would be successful for stable enalapril oral liquid formulations

compositions, ***much less any expectation that the combination of with enalapril, citric acid, sodium citrate, sodium benzoate, sucralose, and water at the recited concentrations*** and at a pH of less than about 3.5 would be successful in forming a stable enalapril liquid formulation. One would need to consider all of these excipients and, through trial-and-error, determine whether each and every one of these components was necessary for stability or if they could be varied or eliminated. Simply put to arrive at ***the combination of these specific components*** using the '747 patent, Nahata, Bicitra, Ora-sweet, and Rippley, one skilled in the art must 'vary all parameters or try each of the numerous possible choices' of the references without 'direction as to which of the many choices is likely to be successful'") (emphasis added); *id.* at 19 ("Applicant … submits that the subject matter in the claims have unexpected results with respect to stability of present enalapril liquid formulations."); *id.* ("the claimed stable enalapril liquid formulations are dramatically much more stable than the extemporaneous enalapril preparations of Nahata and the reconstituted enalapril formulations of the '747 patent"); *id.* at 22 ("Nowhere does the prior art teach or suggest that ***a combination of enalapril, citric acid, sodium citrate, sodium benzoate, sucralose and water at the recited concentrations*** and at a pH of less than about 3.5 at the claimed concentrations would have resulted in such a dramatic stabilization of enalapril") (emphasis added); '008 Patent PH, 2/3//2017 Declaration of Gerold Mosher Under 37 C.F.R. § 1.132 at ¶ 9 ("***The present oral liquid formulations contain enalapril, sucralose, a citric acid buffer, sodium benzoate and water*** at a pH of less than 3.5") (emphasis added); '008 Patent PH, 3/22/2017 Amendment/Remarks at 5 ("It is the Applicant's understanding that the Examiners appreciated the superior stability ***provided by the components and pH as recited in the claims***") (emphasis added).

Silvergate is estopped from asserting infringement of the Bionpharma ANDA Product under the doctrine of equivalents because it surrendered during prosecution any subject matter beyond the exact qualitative and quantitative composition as claimed in the '442 patent.

C.1.2.6.3. Application of the Doctrine of Equivalents is Precluded by the Doctrine of Claim Vitiation.

Applying the doctrine of equivalents to read on the Bionpharma ANDA Product, which does not contain the recited ingredients in the specific recited amounts, would vitiate the "a buffer comprising about 1.82 mg/ml citric acid and about 0.15 mg/mL sodium citrate dihydrate" and "about 1 mg/ml of a preservative that is sodium benzoate" claim elements. Therefore, any assertion of infringement under the doctrine of equivalents is precluded by the doctrine of claim vitiation.

D. Conclusion.

For at least the reasons detailed herein, the claims of the '008 patent, the '745 patent, and the '442 patent are not infringed by Bionpharma's ANDA product, directly or indirectly, literally or under the doctrine of equivalents.

* * * * *

Bionpharma expressly reserves all rights to raise any additional defenses relating to invalidity, unenforceability, and non-infringement, based, *inter alia*, on the facts and information revealed through discovery. Additionally, Bionpharma expressly reserves the right, if sued, to seek a finding of patent unenforceability due to patent misuse. For example, if the '008 patent, the '745 patent, or the '442 patent are asserted against Bionpharma, such an infringement suit would be objectively baseless and a sham, brought for the improper purpose of, *inter alia*, triggering a 30-month stay of Bionpharma's ANDA approval.

II. ABBREVIATED NEW DRUG APPLICATION NO. 212408 OFFER OF CONFIDENTIAL ACCESS PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)

WHEREAS Bionpharma Inc. ("Bionpharma") has provided notice to Silvergate Pharmaceuticals Inc. ("Silvergate") that Bionpharma submitted to the U.S. Food and Drug Administration ("FDA") an Abbreviated New Drug Application ("ANDA") to obtain approval for Bionpharma to engage in the commercial manufacture, use, or sale of enalapril maleate oral solution, 1 mg/mL, that the ANDA has been received by the FDA and assigned ANDA No. 212408, and that the ANDA contained a Paragraph IV certification with respect to U.S. Patent Nos. 9,669,008 ("'008 patent"), 10,039,745 ("'745 patent"), and 9,808,442 ("'442 patent"), which are listed in the FDA Publication, "Approved Drug Products with Therapeutic Equivalence Evaluations";

WHEREAS this document constitutes Bionpharma's Offer of Confidential Access to Silvergate to that ANDA pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III) which provides:

> The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

WHEREAS Bionpharma offers to provide Silvergate confidential access to certain information from its proprietary ANDA ("ANDA Confidential Information") subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA Confidential Information; and

WHEREAS this document accompanies Bionpharma's Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the '008 patent, the '745 patent, and the '442 patent;

NOW, THEREFORE:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions contained in Section 2 below, Bionpharma hereby provides Silvergate this Offer of Confidential

Access ("Offer") to the ANDA for the sole purpose of determining whether to bring an action with respect to the '008 patent, the '745 patent, or the '442 patent;

2. This Offer is subject to the following restrictions as to persons entitled to access and the use and disposition of any information accessed:

A. Persons Entitled to Access: Persons entitled to access to ANDA Confidential Information ("Authorized Evaluators") under this Offer are restricted to outside counsel engaged or employed by Silvergate to represent them and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that such outside counsel has been identified to Bionpharma in writing, and provided said outside counsel does not engage, formally or informally, in any patent prosecution or any FDA counseling, litigation or other work before or involving the FDA.

B. Materials Accessible by Authorized Evaluators: A copy of the ANDA Confidential Information, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.

C. Use of the ANDA Confidential Information:

i. The ANDA Confidential Information and all information contained therein or derived therefrom may be used for the sole and limited purpose of evaluating possible infringement of the '008 patent, the '745 patent, or the '442 patent and for no other purpose. By way of non-limiting example only, the ANDA Confidential Information shall not be used to prepare or prosecute any future or pending patent application, or in connection with any filing to, or communication with, FDA relating to the ANDA.

ii. Authorized Evaluators shall not disclose any ANDA Confidential Information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any ANDA Confidential Information, to any person other than Authorized Evaluators.

iii. Notwithstanding the provisions of subsections 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Silvergate whether or not to bring suit alleging infringement of the '008 patent, the '745 patent, or the '442 patent; provided, however, that the ANDA Confidential Information is not thereby disclosed.

D. Disposition of the Information in the ANDA:

i. Silvergate agrees that if no suit is filed against Bionpharma alleging infringement of the '008 patent, the '745 patent, or the '442 patent within 45 days of receipt of this Offer, Silvergate shall cause Authorized Evaluators, within 30 days after the expiration of the 45-day period, to

destroy or return to Bionpharma the ANDA Confidential Information and all notes, analyses, studies or other documents to the extent that they contain ANDA Confidential Information, and Silvergate shall promptly notify Bionpharma that this has been done.

ii. Silvergate agrees that if an action is filed against Bionpharma alleging infringement of the '008 patent, the '745 patent, or the '442 patent within the 45-day period:

a) While the litigation is pending, the ANDA Confidential Information and all notes, analyses, studies or other documents to the extent that they contain ANDA Confidential Information, shall be maintained in accordance with Sections 2.A and 2.C of this Offer, pending entry of a protective order in the action governing the confidentiality of the ANDA Confidential Information.

b) No ANDA Confidential Information shall be included in any publicly available complaint or other publicly available pleading.

c) Silvergate shall cause Authorized Evaluators to destroy or return to Bionpharma the ANDA Confidential Information provided and all notes, analyses, studies or other documents prepared to the extent that they contain ANDA Confidential Information, within thirty (30) days after the final determination of the action brought against Bionpharma, or as otherwise prescribed in any protective order entered in the action that governs the confidentiality of the ANDA Confidential Information.

E. Accidental Disclosure: Should ANDA Confidential Information be disclosed, inadvertently or otherwise, Silvergate shall, at their earliest opportunity, by and through Authorized Evaluators, contact Bionpharma and identify:

i. what has been disclosed;

ii. the individuals to whom such information has been disclosed; and

iii. steps taken by Silvergate and Authorized Evaluators to ensure the ANDA Confidential Information is not further disseminated.

3. Silvergate acknowledges that violation of any provision of this Offer will cause irreparable injury to Bionpharma and that an adequate legal remedy does not exist. Bionpharma, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Silvergate from violating the terms of this Offer. Silvergate agrees that in such an action Bionpharma is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.

4. Should any provision set forth in this Offer be found by a court of competent jurisdiction to be illegal, unconstitutional or unenforceable, the remaining provisions shall continue in full force and effect.

5. Nothing contained herein shall be construed as a grant of any license or other right to use the ANDA Confidential Information except for the purpose expressly stated herein.

6. When accepted by Silvergate, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.

7. This Agreement shall be construed in accordance with the laws of the State of Delaware without regard to its conflict of law provisions.

8. Nothing in this Offer shall be construed as an admission by Bionpharma regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Bionpharma with respect to the competency, relevance, or materiality of any such ANDA Confidential Information, document, or thing. The fact that Bionpharma provides ANDA Confidential Information upon request by Silvergate shall not be construed as an admission by Bionpharma that such ANDA Confidential Information is relevant to the disposition of any issue relating to any alleged infringement of the '008 patent, the '745 patent, or the '442 patent, or to the validity or enforceability of the '008 patent, the '745 patent, or the '442 patent.

9. Silvergate may request access to the ANDA Confidential Information by executing a copy of this Offer where indicated and returning the executed copy to: Brian P. Murray, Esq., Taft Stettinius & Hollister LLP, 111 E. Wacker Drive, Suite 2800, Chicago, Illinois, 60601-3713. Thereupon, the terms contained in this document shall be considered an enforceable contract between Bionpharma and Silvergate.

Bionpharma Inc.

By their Counsel:

_____

Taft Stettinius & Hollister LLP

Brian P. Murray, Esq.

Dated:

Silvergate Pharmaceuticals Inc.

By its authorized agent:

Signature: _____

Name (Print): _____

Title: _____

Date: _____